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Comparison of tobramycin 80 mg (IV-preparation) and 300 mg solution inhaled twice daily for chronic *P. aeruginosa* infection

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Aims: In an open study with a crossover design we have compared the effect of continuous twice daily administration of 80 mg tobramycin to that of intermittent administration of 300 mg tobramycin in CF patients chronically infected with *P. aeruginosa*.
Methods: All subjects received colistin (1 Mill U b.i.d.) for 3 months before being randomly allocated to either 80 mg or 300 mg of tobramycin b.i.d. After 3 months, patients were switched to the alternative treatment regimen. Lung function and sputum bacteriology were assessed before and after each treatment cycle. Patient preference of the different treatment regimens was also documented.
Results: 32 patients (mean age ± SD: 18.5 ± 8.6 years) completed the trial. There was no difference in age, sex or lung function at baseline between the groups. 18 patients were initially treated with low dose and 14 patients with high dose tobramycin. Compared to the treatment period with colistin, mean (SD) FEV1 decreased by -2.1 (14) % in the low dose tobramycin group and increased by 1.4 (12.5) % in the high dose group. Similar changes were observed for FVC (-2.3 vs. + 2.1%). Variability in responses was large and these differences failed to reach statistical significance. Of the 32 patients completing both treatment arms 19 preferred the higher dose of tobramycin, 7 the lower dose of tobramycin, 3 colistin, whereas 3 had no preference.
Conclusions: A trend towards better lung function was observed for the 300 mg tobramycin group that failed to reach statistical significance. Most patients preferred the higher dose of tobramycin formulated for inhalation to the lower dose preparation.
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Intra-pulmonal deposition of two different tobramycin formulations

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For patients with cystic fibrosis, therapy of chronic pseudomonas aeruginosa infection is essential to improve their quality of life and the course of their disease. Thus a time and cost efficient inhalation of Tobramycin, in an acceptable drug concentration, is crucial. Currently, the most used Tobramycin for inhalation is TOBI®.
The aim of the study was to determine, that inhalation of GERNEBCIN® (Infectopharm), combined with a lower filling dose, would result in a comparable lung deposition of drug substance when supplied with the AKITA device, which has a much higher deposition efficiency compared to conventional nebulizers.
In this randomized cross-over study, 6 healthy subjects inhaled 300 mg TOBI®, filling volume 5 ml, using a Pari Turbo Boy N®/LC Plus and 160 mg GERNEBCIN®, filling volume 4 ml, using AKITA System/Pari LC Star.
Inhalation of TOBI® (5 ml/300 mg) results in 34 ± 7 mg deposition of Tobramycin in the lungs, while inhalation of GERNEBCIN® (4 ml/160 mg) results in 50 ± 5 mg deposition in the lungs. Time to deposit 1 mg in the lungs was not significantly different (TOBI®: 0.33 min/mg, GERNEBCIN® 0.40 min/mg).
Compared to the inhalation of TOBI® the drug amount deposited in the lungs was significantly higher for GERNEBCIN® and costs for depositing one gram were much lower (TOBI 1.60€/mg deposited, GERNEBCIN 0.36€/mg deposited). By pre-setting the dosage via a patient individualized smart card the equivalence dose to Tobi can be set. The lower drug concentration in GERNEBCIN® might also lead to a higher acceptance in CF patients, because of the lesser oropharyngeal irritations.

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Effect of TOBI continuous therapy on pulmonary function in CF patients

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Introduction: The clinical course of CF lung disease correlates with the acquisition of *P. aeruginosa* (Pa) chronic infection.
TOBI (tobramycin nebuliser solution) is licensed for the long term management of chronic respiratory pseudomonal infection.
Aim: To asses the effects of TOBI on pulmonary function in CF patients chronically infected with Pa.
Subjects and methods: We studied seventy clinically stable patients (35 M), median age 22.5 yrs (range 7-41 yrs), 28 homozygous for DF508, mean age Pa colonization 12,9 yrs (range: 2-25 yrs). Replacing a different inhaled antibiotic, 70 pts performed TOBI (300 mg bid, every other month) for 1 year and 51 for 2 yrs. Calculating the annual changes of FEV_1 values ($DFEV_1$), we compared the mean values of the 3 yrs preceding TOBI therapy to the ones during treatment (paired t test). Based on annual $DFEV_1$, we divided our patients into 3 subgroups: worsened (W) (change < -2%), unchanged (U) (between –2 and +2%) and improved subjects (I) (> + 2 %). We compared the prevalence of patients in each subgroup with and without TOBI treatment (chi square analysis). P value less than 0.05 was considered as significant.
Results: The mean (± SD) annual $DFEV_1$ are shown in the table below.

NO TOBI		TOBI	
3-2th yrs	2-1st yrs	0-1st yrs	1-2th yrs
-2.5 ± 8.4	-3.3 ± 8.2	* +0.6 ± 8.6	-0.9 ± 8.8

* $p < 0.02$

During TOBI therapy, the prevalence of W pts is significantly lower than the one in the years without TOBI (42% vs. 56%, $p<0.05$).
Conclusion: Our results, according to literature, suggest that TOBI therapy can reduce pulmonary function decline in CF patients with chronic Pa infection; this could be related, beside its antimicrobial activity, to an action on CFTR function.

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2MU (160MG.) Colistimethate Twice Daily is a safe Nebulized dose for Adults and Children with Cystic Fibrosis

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The safety of 2MU colistimethate nebulized twice daily in patients aged 8 years and above was investigated in a phase I study, with emphasis on tolerability including markers of renal tubular damage (urinary N-acetyl-β-glucosaminidase (NAG) and urinary α-1-microglobulin (a1m)).
12 patients aged 8 years and above with cystic fibrosis and lung infection with P.aeruginosa, were given 2MU colistimethate nebulized twice daily for 28 days. Clinical safety of inhaled colistimethate was evaluated using spontaneously reported and solicited events from a checklist and diary cards. Pulmonary function was measured pre and post therapy.10 patient's data are presented.
Age ranged from 10.5 to 54.6 years (mean=25.3y). 4 patients had received colistimethate 1MU twice daily and 6 patients 2 MU twice daily prior to the study. The commonest reported events were chest tightness, wheezing and cough, but were not reflected by objective change in PFT. The mean pretreatment %predicted FEV1 was 69.0% and was 70.8% at 28 days. Pretreatment dose did not affect outcome.
The mean calculated creatinine clearance was 97.3ml/min pre-treatment and 94.2 post treatment. There was marked inter and intra patient differences in markers of renal tubular damage. Mean urinary creatinine changed from 11.7(S.D. = 5.0)mmol/l to 9.3(S.D .= 5.8)mmol/l. Mean urinary NAG/creatinine ratio was almost unchanged from 23.4(S.D. = 32.3) to 22.1(S.D. = 9.8) U/mmol creatinine. Mean a1m/creatinine ratio changed from 0.53(S.D. = 0.27) to 1.14(S.D.= 0.94) mg/mmol creatinine.
No patient discontinued nebulized colistimethate therapy due to untoward event or abnormal laboratory findings.
These limited data suggest that nebulizing 2MU colistimethate twice daily is a safe therapy for patients with cystic fibrosis.